

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

β,β -Pentamethylene Butyrolactone

We, WARNER - LAMBERT PHARMACEUTICAL COMPANY, a corporation organized under the laws of the State of Delaware, United States of America, of 201 Tabor Road, Morris Plains, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new and novel method of preparing β,β -pentamethylene butyrolactone which has the structure:



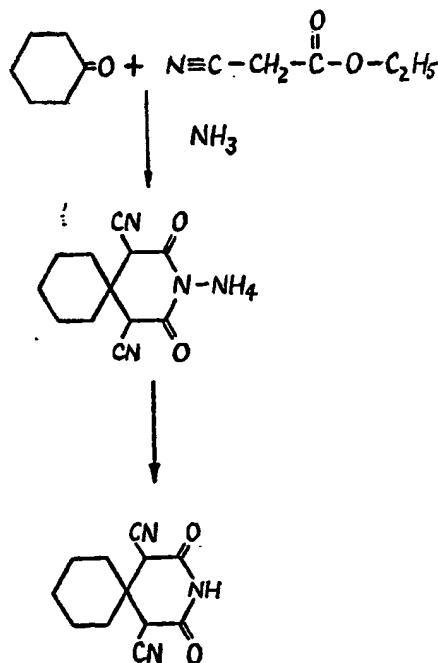
The β,β -pentamethylene butyrolactone and the salts of 3,3 - pentamethylene - 4 - hydroxy-butyric acid produced therefrom by the method described and claimed in copending application 3225/62 (Serial No. 897,931) are useful as central nervous system stimulants having a high therapeutic index.

These products are pharmaceutical products particularly valuable as central nervous system stimulants of high therapeutic index and which may be used for oral and parenteral administration in effective dosages without producing undesirable side effects. They are especially useful as analeptic agents which may be used for combatting excessive hypnosis such as that resulting from an overdose of barbiturates and also as respiratory and cardiovascular stimulants.

β,β -Pentamethylene butyrolactone is disclosed by Windaus et al, Ber. 55B, 3981 (1922). This compound may be produced in accordance with the techniques of the prior art in the following sequence of steps starting with cyclohexanone:

Step I

Thorpe, J. Chem. Soc. (London) 115,686—704 (1919) discloses the reaction of cyclohexanone, ethylcyanoacetate and ammonia in the molar proportions of 1:2:3 (50 per cent excess of ammonia) in alcoholic solution at a temperature of about 40° C. to form the ammonia salt of α,α^1 - dicyano - β,β - pentamethyleneglutarimide which in turn is reacted with HCl to form the free imide.



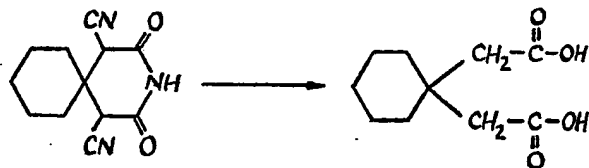
α,α^1 -dicyano- β,β -pentamethyleneglutarimide. 50

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Step II

Thorpe, J. Chem. Soc. (London) 99, 445-446 (1911) discloses the hydrolysis of α, α' -dicyano- β, β -pentamethyleneglutarimide by dissolving this compound in concentrated sulfuric acid, diluting the solution

with water, heating the mixture for 1 hour at 190° C. diluting again, boiling for 5 hours and separating cyclohexanediactic acid from the mixture by repeated extraction with ether.

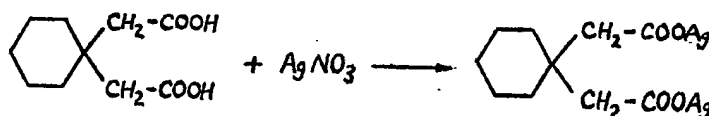


Cyclohexanediactic acid

Step III

By conventional techniques of salt forma-

tion, the di-silver salt of cyclohexanediactic acid is formed.

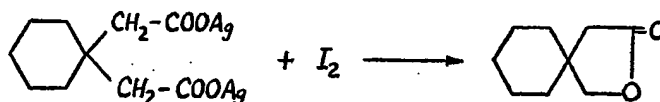


di-silver cyclohexanediacetate

Step IV

Windaus, Ber 55B, 3981 (1922) discloses the conversion of the di-silver salt of cyclohexane diacetic acid to β, β -pentamethylene

butyrolactone by reaction of the salt with iodine in the presence of sand followed by extraction with ether.



The above described method of preparing β, β -pentamethylene butyrolactone from cyclohexanone is attended with certain disadvantages, particularly in large scale commercial production. Yields in Step I are only about 30 per cent of theory and the purity of the intermediate ammonium salt is such that conversion to the imide is necessary prior to hydrolysis to cyclohexanediactic acid. In the final step involving the reaction of the di-silver salt of cyclohexanediactic acid with iodine, the use of sand as a diluent for the reaction mixture is cumbersome. In addition, yields in this reaction by the method of the prior art are low and the purity of the final product β, β -pentamethylene butyrolactone is reduced due to the presence of cyclohexanediactic acid anhydride which forms an azeotropic mixture with the desired lactone. The over-all yield of β, β -pentamethylene butyrolactone based on the cyclohexanone charged in Step I by the above method is under 10 percent.

It is an object of this invention to provide a commercially feasible method of preparing β, β -pentamethylene butyrolactone in good yields from cyclohexanone.

Other objects and the advantages of this invention will become apparent from the

following detailed description.

It has now been found that β, β -pentamethylene butyrolactone may be prepared from cyclohexanone in good yields by the process which comprises reacting cyclohexanone with a lower alkyl ester of cyanoacetic acid and with the stoichiometric amount or a slight excess of ammonia at a temperature of less than 0° C. to form the ammonium salt of α, α' -dicyano- β, β -pentamethyleneglutarimide, hydrolyzing the ammonium salt to cyclohexane-diacetic acid by the portion-wise addition of the ammonium salt to concentrated sulfuric acid, converting the cyclohexanediactic acid formed to the corresponding di-silver salt thereof, and, in accordance with the present invention, finally reacting the di-silver salt with iodine at a temperature of between about 150° C. and about 170° C. in the presence of benzene, toluene or xylene. The method of this invention represents a marked improvement over the method of the prior art as described above both in terms of an over-all simplification of the reaction sequence and in terms of a markedly improved yield of the desired β, β -pentamethylene butyrolactone. The over-all yield of finished product is in excess of 40 per cent of theory based on the cyclo-

hexanone supplied to the initial step in the reaction sequence. This yield is far superior to the yield of under 10 per cent obtained by the method of the prior art.

5 The initial step in the reaction sequence of this invention involves the conversion of cyclohexanone to the ammonium salt of α,α^1 -dicyano - β,β - pentamethyleneglutarimide. Cyclohexanone is reacted with a lower alkyl
10 ester of cyanoacetic acid and ammonia in the molar proportions of 1 mol of cyclohexanone to 2 mols of the lower alkyl ester of cyanoacetic acid to between 2 and 2.5 mols of ammonia. The term "lower alkyl"
15 as used herein includes those straight and branched chain aliphatic hydrocarbon groups having from 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-amyl and n-hexyl. It has been found
20 preferable to use ethyl cyanoacetate as a reactant with cyclohexanone and ammonia.

The reaction is preferably carried out in an alcohol solution of the reactants. It is essential that the reaction be carried out, at
25 least initially, at a temperature of 0° C. or below. A temperature of between 0° C. and -10° C is preferred. The solution of the reactants in a solvent such as ethyl alcohol is allowed to react at said temperature for
30 between about 1 and about 3 days. At the conclusion of this initial phase of the reaction, the temperature may be permitted to rise to room temperature and the reaction allowed to proceed for several additional days
35 after which the precipitated ammonium salt of α,α^1 - dicyano - β,β - pentamethyleneglutarimide which forms is separated from the reaction mixture by filtration or centrifugation.

40 It has been found that in the above reaction the ammonium salt of α,α^1 -dicyano- β,β -pentamethyleneglutarimide is obtained at a yield of between 95 and 98 per cent of theory based on the amount of cyclohexanone
45 charged to the reaction vessel. This represents a marked improvement over the yield obtainable by the method of the prior art which is generally no higher than 30 per cent. Although the same intermediates are
50 reacted as in the method of the prior art, the remarkable improvement in the yield is believed due both to the lower temperature maintained during the initial phase of the reaction, and also to the use of only a slight
55 excess of ammonia in the reaction mixture. In the method of the prior art 3 mols of ammonia are used per mol of cyclohexanone constituting a 50 per cent excess of the theoretical amount. In this method the
60 ratio of ammonia employed is maintained between 2 and 2.5 mols per mol of cyclohexanone. Not only is the yield of the ammonium salt of α,α^1 - dicyano - β,β - pentamethyleneglutarimide high, but the ammonium
65 salt formed is of high purity which

greatly simplifies the following steps in the reaction sequence.

The second step in the process involves the hydrolysis of the ammonium salt of α,α^1 -dicyano - β,β - pentamethyleneglutarimide to cyclohexane-diacetic acid. The hydrolysis is
70 preferably carried out in a concentrated sulfuric acid which contains between about 80 and about 90 per cent sulfuric acid by weight. The concentrated sulfuric acid is first heated
75 to a temperature of between about 120° C. and about 140° C. and the ammonium salt of α,α^1 - dicyano - β,β - pentamethyleneglutarimide is then added portion-wise to the acid. During the hydrolysis carbon dioxide and
80 sulfur dioxide are evolved. Each successive portion of the ammonium salt is added after the gas evolution resulting from the addition of the preceding portion has substantially
85 ceased. Due to the heat liberated during the exothermic hydrolysis, the temperature of the reaction mixture increases to between about 160 and 180° C. which is the desired reaction temperature. No external heating or
90 cooling is therefore necessary when the ammonium salt is added portion-wise as described above. At the conclusion of the addition of the ammonium salt the mixture is allowed to stand for a short time at the
95 above reaction temperature, and is thereafter cooled to induce crystallization of the cyclohexanediacetic acid formed.

It has been found that a yield of about
75 per cent based on the quantity of the ammonium salt of α,α^1 - dicyano - β,β - pentamethyleneglutarimide charged is obtained. This method represents a substantial improvement over the method of the prior art. In the latter method the ammonium salt
100 of α,α^1 - dicyano - β,β - pentamethyleneglutarimide is initially hydrolyzed with hydrochloric acid to the corresponding free imide prior to the hydrolysis with sulfuric acid. In the present method, the portion-wise
105 addition of the ammonium salt to the concentrated acid is of advantage in that it simplifies the problem of temperature control during the reaction.

The third step in the reaction sequence is conventional and involves the conversion
115 of cyclohexanediacetic acid to its corresponding di-silver salt. Any of the conventional techniques for forming metal salts of organic acids may be employed. For example, cyclohexanediacetic acid in the presence of a slight
120 excess of ammonia may be reacted with a soluble silver salt such as silver nitrate and the resulting precipitate comprising the desired di-silver salt of cyclohexanediacetic acid is recovered from the solution by filtration
125 or other means.

The final step in the reaction sequence, which is the process of the present invention, involves the conversion of the di-silver salt
130 of cyclohexanediacetic acid to β,β -penta-

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methylene butyrolactone. This reaction is carried out by reacting the di-silver salt with iodine in the relative molar proportions of about 1 mol of the di-silver salt to 1 mol of iodine. It has been found that this reaction may be carried out with ease and efficiency in the presence of benzene, toluene or xylene.

Normally, about 2 to about 4 parts by weight of solvent per part of reactants is used. The reaction mixture is then heated to a temperature of between about 150 and 170° C. and maintained at the reaction temperature for about 3 to about 10 hours. At the conclusion of the reaction the mixture is processed for the recovery of β,β -pentamethylene butyrolactone therefrom. This recovery is most conveniently effected by treating the reaction mixture at a temperature of between about 90° C. and 110° C. with a dilute solution of alkali such as sodium hydroxide containing a slight molar excess of alkali based on the amount of iodine initially charged to the reaction mixture. The resulting aqueous phase is separated, acidified, heated, cooled, and extracted with a suitable organic solvent such as benzene. Any unreacted cyclohexanediactic acid is removed by filtration and the finished product is recovered after evaporation of the extracting solvent by distillation under vacuum.

The method of this invention for converting the di-silver salt of cyclohexanediactic acid to β,β -pentamethylene butyrolactone represents a marked improvement over the techniques of the prior art for carrying out the same reaction. It has been found that over-all yields of between 60 and 80 per cent of theory are obtainable in the reaction, whereas the technique of the prior art for carrying out the same reaction results in the yield of only about 40 per cent of theory. In addition, control of the reaction temperature and recovery of the product from the reaction mixture is markedly simplified by the method of this invention as compared to the method of the prior art where the reaction is carried out in the presence of sand. It has further been found that the purity of the product produced by the method of this invention is considerably higher than that obtainable by the method of the prior art.

The product β,β -pentamethylene butyrolactone may be used therapeutically in this form or alternately may be converted to therapeutically active salts such as the alkali metal, alkaline earth metal, ammonium and amine salt.

The following example illustrates the method of this invention.

EXAMPLE

Step A

10.2 kg. cyclohexanone and 23.5 kg. ethyl cyanoacetate are mixed and cooled to -10°

C. 3540 grams of ammonia are dissolved in 96 per cent (denatured) alcohol as an 11 per cent solution of ammonia and also cooled to -10° C. The ammonia solution is added to the mixture of cyclohexanone and ethyl cyanoacetate with constant agitation and cooling so that the temperature remains below 0° C. during the addition. The molar ratio of the reactants is 1 mol cyclohexanone to 2 mols ethyl cyanoacetate to 2 mols ammonia. After the addition of all the ammonia solution, the mixture is allowed to stand for two days at 0° C. and then for an additional three days at room temperature. Crystals which form are separated from the reaction mixture by centrifugation, washed with ether and dried in air at 40° C. A yield of 24.3 kg of the ammonium salt of α,α' -dicyano- β,β -pentamethyleneglutarimide is obtained, which is 96 per cent of theory.

Step B

A mixture of 60 litres of 96 per cent sulfuric acid and 16 liters of water is heated to 130° C. The 24.8 kg. of the ammonium salt of α,α' -dicyano- β,β -pentamethyleneglutarimide obtained in Step A is added intermittently and in small portions to the hot sulfuric acid solution. After the addition of each portion, the carbon dioxide and sulfur dioxide evolved in the reaction are permitted to escape before the next portion is added. During the portion-wise addition, the temperature of the reaction mixture increases spontaneously to 170° C. After all the ammonium salt has been added, heating is continued at 170° C. for one hour, and then the reaction mixture is allowed to cool overnight. The brownish-black crystals of cyclohexanediactic acid which form are separated from the reaction mixture by centrifugation, washed twice with water, dissolved in hot alcohol and filtered hot. The filtrate is allowed to stand over-night and crystals of cyclohexanediactic acid are removed by filtration and dried. A yield of 15 kg. of cyclohexanediactic acid representing 75 per cent of theory is obtained.

Step C

585 grams of cyclohexane diacetic acid prepared as described in Step B are suspended in 6.6 liters of water, and 438 ml. of 25 per cent aqueous ammonia is added. The mixture is stirred until the cyclohexanediactic acid dissolved. The solution is filtered and added to 994 grams of silver nitrate dissolved in 1.5 liters of water. The resulting precipitate of the di-silver salt of cyclohexanediactic acid is recovered by filtration and washed with water until the wash water is free of nitrate ion. The resulting white precipitate is dried in vacuum at 60° C. in the dark, and weighs 1140 grams, representing a yield of 94.3 per cent of theory.

Step D

263 grams of the di-silver salt of cyclohexanediactic acid prepared as described in Step C is finely pulverized and mixed with 156 grams of iodine and 1000 grams of benzene. This represents a molar ratio of the di-silver salt to the iodine of 1 to 1. The mixture is vigorously stirred and heated to a temperature of 160° C. and held at this temperature for 5 hours. The reaction mixture is then cooled to 90° C. and 260 ml. of 10 per cent aqueous sodium hydroxide solution is added. The mixture is stirred and heated to about 110° C., the boiling point of the aqueous phase. The resulting mixture is cooled, the aqueous phase is separated, and the organic phase heated again to 110° C. with 80 ml. of 10 per cent aqueous sodium hydroxide solution. The combined aqueous phases are filtered, acidified with hydrochloric acid, heated to 90° C. and then cooled. The organic phase is separated and the aqueous phase is extracted several times with benzene. The benzene extracts are then combined with the separated organic phase. The precipitate which constitutes unreacted cyclohexanediactic acid is removed by filtration and the filtrate is further purified by extraction with an aqueous dilute sodium bicarbonate solution. The purified benzene phase is dried over anhydrous magnesium sulfate, filtered and the solvent removed by distillation. The product obtained, β,β -pentamethylene butyrolactone, after purification by distillation twice under vacuum has a boiling point of 135 to 138° C. at 12 millimeters. A yield of 65 per cent of theory is obtained.

Toluene and xylene were effectively used

as reaction media in place of benzene in the process described in Step D of the Example.

The foregoing example illustrates the production of β,β -pentamethylene butyrolactone from cyclohexanone with an over-all yield of 44 per cent of theory based on the amount of cyclohexanone charged to the reaction vessel in Step A. This yield is a substantial improvement over the yield of less than 10 per cent of theory obtained by the method of the prior art, with a result that the method of the present invention is feasible in a commercial operation. The method of the invention also represents a simplification in the individual process steps of the method of the prior art.

WHAT WE CLAIM IS:—

1. A process for preparing β,β -pentamethylene butyrolactone which comprises reacting a di-silver salt of cyclohexane diacetic acid with iodine at a temperature of between about 150° C. and about 170° C. in the presence of benzene, toluene or xylene.
2. A process according to claim 1, in which about 2 to about 4 parts of the solvent by weight per part of the di-silver salt and iodine are employed.
3. A process for preparing β,β -pentamethylene butyrolactone substantially as described herein with particular reference to the example.
4. β,β -Pentamethylene butyrolactone whenever prepared by a process according to any of the preceding claims.

STEVENS, LANGNER, PARRY
& ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.